IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellants:	Richard P. Batycky, Giovanni Caponetti, Mariko Childs, Elliot Ehrich, Karen Fu, Jeffrey S. Hrkach, Wen-I Li, Michael M. Lipp, Mei-Ling Pan and Jason Summa		
Application No:	10/607,571	Group No:	1616
Filed:	June 26, 2003	Examiner:	J. H. Alstrum Acevedo
Confirmation No.:	6287		
Title:	INHALABLE EPINEPHRINE		

APPEAL BRIEF

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Sir:

This Reply Brief is filed in response to the new arguments made in the Examiner's Answer. These new arguments for each ground of rejection are set forth under separate headings.

A. *Claims 140-143, 153, and 156-160 are finally rejected under 35 U.S.C. §103(a) as being unpatentable over Tarara (US 2005/0074498) in view of Slutsky (U.S. Pat. No. 6,102,036).*

In essence, the rejection relied on Tarara to teach powders for inhalation and Slutsky to teach an inhaler to administer the powders. The Examiner argued that it would be obvious to administer Tara's powders via Slutsky's inhaler and, in doing so, one would arrive at the claimed invention. Appellants disagreed, in essence, explaining that (1) Tarara did not teach the claimed powders, (2) Slutsky's inhaler does not cure the deficiencies of Tarara and (3) one would not select Slutsky's inhaler for use with the

claimed powders. The failings of each reference for what the Examiner asserted the reference taught was explained in detail under a separate heading and then the combination of references was also explained in detail. In view of this brief summary of the appellate record to date, the Examiner's specific new issues will be discussed. These new issues are raised in the Answer beginning at Page 18.

In summary, Appellants argued that Tarara provides FPF data for powders that are dispersed by a proprietary inhaler employing pressurized propellants, not a patient's breath. High FPF's were achieved by Tarara after 20 or more actuations. The raw data simply does not support the Examiner's argument that these powders would necessarily possess an FPF of at least 45% upon a single breath activated step. This data was analyzed from multiple directions. Further, when one reads the generic disclosure relating to FPFs *in light of the experimental section*, again, one would not conclude that high FPFs are obtainable in a single breath-activated step. Appellants also pointed out that Slutsky does not teach that its inhaler can achieve these results with any powder, much less Tarara's.

The Examiner dissects, restates, albeit incorrectly, and numbers the dissections as arguments (2) and (7), on Page 18 of the Answer, dismissing the argument by stating that arguing the references individually when the rejection is based on a combination does not establish nonobviousness. Notably, Appellants argued that neither reference teaches the delivery of a high FPF with a single breath activated inhaler. Tarara teaches that a high FPF is achieved only with 20 actuations of an inhaler using a propellant. Slutsky does not teach that its inhaler achieves a high FPF with any powder. The Examiner ignores the context of the full argument and only states that the argument is that Tarara does not exemplify a breath activated inhaler and Slutsky is silent on the FPF limitation. That is not an accurate restatement of the argument. The argument goes to what is meant by Tarara by a high FPF and that it does not teach the entire *claim limitation*. The Examiner's dissection of the argument and limitation into two parts (FPF as measured using any inhaler and any method) and then using a specific class of inhalers for the claimed delivery step is error. It is only when the Examiner ignores the limitation as a whole and dissects it into two separate quips.

In any event, Appellants discussed each reference individually first. However, the combination of references was also discussed. Notably, where, as here, the *same* limitation

is *not* taught by *either* reference, the limitation is simply not taught by the combination. Thus, the Examiner's dismissal of the arguments is in error.

A fundamental issue on this appeal is the meaning of "fine particle fraction" or "FPF" (usually referring to the mass that is dispersed and deposited in an impactor) in these claims and in each reference. The Examiner assumes that the meaning of "FPF" is identical in each document and that it is not related to the manner in which the powder is dispersed or how the particles are delivered to the impactor. This assumption is illogical. The manner in which a test is done frequently impacts the result. That is obviously true in this case. Additionally, understanding the basis for the calculation is important. The FPF can be measured as the percent of the mass that is deposited on selected stages of the impactor (usually identified as correlating to a diameter) on the basis of the total amount of drug loaded into the impactor or into the inhaler. One must analyze the terms of the claim reading the instant specification. One must read the terms of the prior art reading that specification. Even where the terms are the same, their meaning can be different. That is the case here.

Turning to what the Examiner viewed as a different argument (1), Appellants' explained that the data presented in Tarara relating to the efficiency of delivery of the powders simply did not make sense. Appellants concluded that, as a result, Tarara did not teach the person of skill in the art powders of the claimed invention. The Examiner dismisses the point, stating that errors in the math of an example do not justify "wholly dismissing" the remaining generic teachings. Appellants agree that an error in math in an example generally does not justify dismissing the teachings of an entire patent application. However, where, as here, one needs to look to the examples to understand what the terminology (FPF, for example) means, the fact that the data does not add up is highly relevant. A patent is read as a whole. The data in an example informs the reader how to interpret the generic disclosure and the terms used. The Examiner, on the other hand, feels free to ignore the data in the patent as it suits him and to interpret the generic disclosure in his own way.

The simple issue is that, yes, Tarara teaches high FPFs in the generic disclosure. The question, however, is how does the patent define the term, FPF, and how does that compare to the FPF limitation in the claim, *as that term is defined by this specification*.

Are the prior art FPFs calculated after 20 actuations with a propellant in an undisclosed proprietary inhaler and, if so, how is the calculation performed? By the methods in the examples, which the Examiner admits appear to be wrong? Or are we to simply assume, as the Examiner does, that high FPFs will also be achieved by Tarara's powders using a breath activated inhaler, such as Slutsky's, after a single inhalation? Appellants do not believe that a person of skill in the art would assume that a single breath activated inhalation (which generally applies less dispersion energy) will be equivalent to or exceed a propellant-based inhaler after 20 actuations. Appellants believe that the FPF should be read as measured by the methods described in the examples. However, these methods do not provide a mass balance. This problem makes understanding the generic disclosure difficult. Simply, Tarara provides no evidence that he achieved powders having the characteristics generically described therein, the terms are synonymously used in the instant specification and prior art and there is no reason to believe that they would inherently possess the claimed characteristics. The Examiner "cherry picks" sentences from the reference to make his case, ignoring the context of the reference. Rather, the Examiner is charged with the duty of interpreting the reference as whole.

With respect to Appellants' arguments relating to dependent claims 142, 143, 153 and 156-160, the Examiner points to teachings relating to drug loads generally (labeled arguments 9-11). Appellants' arguments relate to epinephrine specifically. The dose prudent for an antibiotic will not be the same as a dose for epinephrine. The problems with delivering an antibiotic are not the same as those for delivering epinephrine. Appellants' arguments relate to the combination of epinephrine, drug load and drug dose. Tarara does not teach these selections. The broad ranges offered by Tarara together with the number of drugs and excipients presents a nearly infinite number of possible combinations.

With respect to Claims 156-160, the Examiner suggests that the recitation of the result achieved does not impact the physical characteristics of the product or the method. Of course, the person of skill in the art would not agree and the allegation is not logical. A particle of identical physical characteristics delivered to a patient in identical methods will not primarily target to two different locations in the lung. As is generally known in the art, aerodynamic size of the particles dictates the location of deposition. Thus, a claim that

states the location of deposition implicitly defines the aerodynamic diameter of the product.

The Examiner takes a sentence in the brief relating to tap density out of context and labeled it as argument (8). Simply, the generic disclosure, referenced by the Examiner for teaching "tap density," actually taught "bulk density." These are two different properties. As pointed out in the Answer, two working examples, neither of which is an epinephrine powder, have a tap density in the claimed range. The Appellants' point was not that the reference does not describe anywhere a powder that has a low tap density. The gratuitous sentence that Appellants "overlooked" the tap density in the examples was not appropriate.

Likewise, the Examiner mischaracterizes the argument numbered (3). Appellants did not argue that one of skill in the art would simply not be motivated to select epinephrine for pulmonary delivery. Simply noting that Tarara lists epinephrine in a list is unhelpful and confuses the issue. The issue is whether the person skilled in the art would select epinephrine, envision how to make a highly dispersible powder having the claimed FPF limitations, combine it with a breath-activated inhaler and expect an efficacious therapy. Tarara and Slutsky do not teach the combination.

With regard to the arguments the Examiner numbers as (4)-(6), he states the underlying features are not limitations in the rejected claims. Once again, the Examiner takes the discussions out of context. The burden is on the Examiner to establish motivation to combine references. Where, as here, epinephrine patients for pulmonary delivery are characterized by breathing difficulties (e.g., suffering from anaphylaxis, see rejected Claim 161), one wouldn't be motivated to combine an epinephrine powder with an inhaler designed to further restrict air flow, such as the Slutsky inhalers. The arguments are not directed to missing limitations in the claims. It is directed to the Examiner's underlying assumptions that there is motivation to combine the references.

Backing up, Appellants established that patients in need of pulmonary epinephrine include patients having difficulty breathing, such as patients in anaphylaxis. The Examiner attempted to rebut that evidence by pointing to the ocular delivery of epinephrine to treat glaucoma, reasoning that not all patients in need of epinephrine have difficulty breathing. Assuming that patients in need of pulmonary epinephrine include glaucoma patients, the Examiner infers, without evidence, that the person of skill in the art would be motivated to

treat glaucoma via a pulmonary route, thereby rendering the Slutsky inhaler a viable inhaler for use with Tarara's epinephrine powders. When the Appellants pointed out that the evidence does not support the Examiner's position, the Examiner responded by saying that Appellants have not shown that pulmonary delivery cannot treat glaucoma and the claims do not exclude the treatment of glaucoma. The Examiner, in making these arguments, forgets the simple fact that the initial burden of proof rests with him to show that his rejection relied on the initial assumption that it would have been obvious to treat glaucoma via pulmonary delivery of epinephrine. The burden does not lie with the Appellants to establish that nonobvious uses of epinephrine (pulmonary delivery of epinephrine for the treatment of glaucoma) with the claimed methods would be impossible.

The Examiner now states that the burden is on the Appellants to define the flow rate and resistance of the inhaler within the claim that would permit the claimed method in order to establish non-obviousness. No caselaw in support of this position is offered. The complaint rather smacks of a rejection under 35 USC 112, first paragraph. The specification describes the characteristics of inhalers and powders that will successfully result in the claimed method. As such, the claims are enabled. The invention is based on the discovery of highly dispersible epinephrine powders that can be delivered efficiently to a difficult patient population by a variety of inhalers. The invention is also based on the discovery of a highly efficient inhaler. These two improvements permit a great deal of flexibility in treating a difficult patient population. It is possible that the powders of the claims (which are not the powders of Tarara) can be effectively delivered by the Slutsky inhaler. It is also possible that the powders of Tarara could be successfully delivered with the preferred inhaler of the specification. These combinations have not been tested. But whether or not the Slutsky inhaler can be used to deliver epinephrine in accordance with this specification in light of its teachings is not relevant in anyway to the issue of whether it would have been obvious at the time the invention was made to combine Tarara and Slutsky. The fact is that the prior art does not make obvious the claims and there is no reason for the Appellants to artificially burden the claims with words that positively exclude the Slutsky inhaler.

B. *Claims 161-162 are finally rejected under 35 U.S.C. §103(a) as being unpatentable over Tarara (US 2005/0074498) in view of Slutsky (U.S. Pat. No. 6,102,036) further in view of the PDR.*

No new arguments are raised.

C. *Claims 140-143, 146-150, 159, 160 and 162 are finally rejected under 35 U.S.C. §103(a) as being unpatentable over Foster et al. (US2003/0215512 in view of Tarara (US 2005/0074498)and Slutsky (U.S. Pat. No. 6,102,036).*

The Examiner dismisses Appellants' discussion of the divergent physical properties of the Foster and Tarara products (solid versus hollow), the incompatible excipients (glassy versus phospholipid) used therein, the different problems to be solved (storage stability versus suspension stability), and divergent solutions (selecting specific morphologies and excipients) to these different problems as hypotheses, conjecture and speculation. The Examiner does not actually address the factual issues raised in the Appellants' arguments. Just because an attorney discusses facts and technology does not reduce it to "attorney argument" that can be summarily dismissed.

As above, the Examiner dismisses the Appellants' discussion of Foster's use of the fine particle fraction product feature. As above with Tarara, the Examiner assumes that the mass deposited in an impactor (i.e., FPF) is not related to the manner in which the powder is dispersed or how the particles are delivered to the impactor or how the value is calculated. This assumption is illogical. The manner in which a test is done frequently impacts the result. Clearly, the calculation is important (the percent based on amount of powder delivered to the impactor will be greater than the amount of powder loaded into the inhaler because the former will not include the mass left behind in the inhaler). That is obviously true in this case. One must analyze the terms of the claim reading the instant specification. One must read the terms of the prior art reading that specification. Even where the terms are the same, their meaning can be different. That is the case here.

The Examiner misstates the Appellant's arguments relating to Slutsky, which he numbers (5) and (7). The Examiner asserted that Slutsky teaches that one would be motivated to deliver a dose in the fewest number of administrations. Appellant's disputed

the allegation and explained why (e.g., Slutsky was concerned with delivering too much nicotine too quickly because nicotine is irritating).

The Examiner now argues that the claims, employing the word comprising, do not avoid additional steps. The Examiner concludes that the claims do not limit delivery to a single breath. Firstly, the argument was to rebut the Examiner's initial allegation of motivation to combine. Thus, the Examiner's current point is not relevant in context.

Secondly, the claims state that the administration is in a single breath-activated step. The purpose of the invention is to deliver the dose with efficiency in a single breath. It is agreed that it is possible that a patient may take a second breath through the inhaler. However, the claims require that the first breath deliver at least 45 % of the drug dose. It is believed that, irrespective of whether a second breath can be taken by the patient, there is no motivation to combine and the prior art does not teach the claimed invention.

The Examiner's points on the crystalline state of the particles and excipients with respect to Claims 146-150 on Page 25 of the Answer are well taken.

D. *Claims 163-170 are finally rejected under 35 U.S.C. §103(a) as being unpatentable over Tarara (US 2005/0074498) in view of Slutsky (U.S. Pat. No. 6,102,036) further in view of Warren (1986).*

No new arguments are presented.

E. *Claims 172-173 are finally rejected under 35 U.S.C. §103(a) as being unpatentable over Foster et al. (US2003/0215512 in view of Tarara (US 2005/0074498) and Slutsky (U.S. Pat. No. 6,102,036) further in view of the DIH.*

The Examiner has refused to consider the evidence in Exhibit A. This is believed to be in error. The evidence was referenced and discussed in the Amendment filed on September 3, 2008. While copies were not provided with that amendment, it was certainly discussed, reviewed and considered by the Examiner. Thus, it is believed to be a part of this record and should be considered in this appeal. In any event, the rejection should be reversed even if the evidence is not considered for the reasons of record.

The Examiner dismisses the arguments that explain why Foster does not teach the claimed formulations, stating that, absent evidence that the skilled artisan would suspect

that the claimed combination could not be achieved, the claimed combination is obvious. This is certainly not the proper standard for analyzing obviousness. The Examiner has not (and cannot) show that the legal presumption is that a claimed formulation is obvious absent evidence that the claimed combination is chemically incompatible. Additionally, discussing the technical teachings of Foster and explaining why those teachings are inconsistent with the Examiner's conclusion of obviousness is not "speculative assertion." The Examiner's rejection is tantamount to stating that any pharmaceutical formulation containing any combination of known components in any amount is prima facie obvious, irrespective of what the reference teachings relied upon describe.

The Examiner goes on to state that if, he adopts the Appellants' arguments, he would need to make enablement rejections against every composition claim. This gratuitous and illogical statement confuses the standards for examining a claim for enablement and reviewing a claim for non-obviousness. There is absolutely no reason to conclude that compositions must either lack enablement or be obvious.

Again, the Examiner infers an argument was made that simply was not. Appellants did not argue that one of skill in the art could not make a pharmaceutical composition absent undue experimentation. That does not mean that one cannot invent within the class of pharmaceutical compositions and make a patentable and non-obvious combination. The burden rests with the Examiner to show that a claimed selection is obvious. The Examiner has failed to do so here.

With respect to the Examiner's arguments relating to selecting epinephrine bitartrate simply because it is know, 5% being embraced by "about 11%", sodium tartrate being a glass former (sodium tartrate is not one of only eight glass formers taught by Foster, but Appellants did not analogize the selection of sodium tartrate as picking a needle from a haystack; and the Examiner ignored the low concentration of the glass former), Tarara's erroneous disclosure is a preference which is not a teaching away, have been addressed directly or indirectly in the Brief.

What is striking in this 32 page Answer is the absence of any real discussion of Appellants' arguments. The vast majority of the Examiner's discussion misstates and misrepresents the arguments in the Brief. This Reply Brief is primarily directed to

ensuring that the Board of Appeals does not mistakenly adopt the Examiner's interpretation of the Brief.

The Conclusion

As the Examiner has failed to establish a *prima facie* case of obviousness and the unexpected results achieved by the present invention, Appellants request reversal of the rejections and allowance of the application.

Respectfully submitted,

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